REMARKS/ARGUMENTS

Reconsideration of the subject application and entry of this Amendment are requested. Claims 1, 2, 5, 6, 7, 9-14, 19-24 and 26-38 will be pending subsequent to entry of this Amendment.

The Official Action presents has two issues. Firstly the obviousness objection raised in the last Office Action has been maintained (sections 1 and 11 to 19). Secondly, the Examiner has difficulty with the reference to analogues and derivatives of e.g. calcitonin, growth hormone and parathyroid hormone in claims 9 to 11 and 19 to 21 (sections 3 to 10). These issues are considered in turn.

Obviousness – sections 1 and 11 to 19 of the Office Action

In section 1 the Examiner advises that for formal reasons the Declaration filed with the last response has been ignored. A replacement Declaration is attached, which has been revised as suggested by the Examiner in section 1 of the Office Action.

The obviousness objection relies on the assumption that all antioxidants and preservatives are compatible and equivalent. The accompanying Declaration supports applicant's assertion that this is not sound. In this regard the Examiner's attention is drawn to the comments on pages 10 to 12 of the previous response, dated 5 November 2008. Thus, the obviousness objection should be withdrawn.

It is believed that the obviousness objection should be withdrawn in view of the attached Declaration and the above comments. Notwithstanding that, however, the comments made in the Applicant's last response are maintained, and some additional comments in connection with the Examiner's discussion in section 19 of the Office Action now follow.

In the first paragraph of section 19 the Examiner argues that the effect of the PG/BHA is not recited in the rejected claims. Then, on page 17, she suggests that although the effect of the PG/BHA is recited in claim 38, the effect is not limiting because the claim does not require the effect to be realized.

Firstly, please note that claim 26 does recite the effect of the PG/BHA. Thus, claim 26 is to a method, and states: "*...which method enhances the absorption of the active macromolecular principle due to the additive improving the solubility of the bile salt*". Thus, claim 26 does require the effect to be realized and so the Examiner's objection does not apply to claim 26.

Secondly, composition claim 38 has now been amended to specify that the composition is an oral pharmaceutical composition. Thus, claim 38 covers compositions that are destined to be administered orally, and so will inevitably entail realization of the effect of the PG/BHA. Thus, the objection also does not apply to claim 38.

Towards the end of the first paragraph in section 19 the Examiner alleges that sodium bicarbonates are often added to hydrophobic amines. This is apparently prompted by the comments in the Applicant's response of 5 November 2008 (pages 10 to 12) on the incompatibility of sodium bicarbonate and PG/BHA.

This point should become moot in view of the attached Declaration, which confirms the previously discussed incompatibility. However, for completeness applicant would highlight that PG and BHA are clearly not hydrophobic amines. Indeed, they are rather different. However, a detailed comparison is impossible because the point made by the Examiner has not been properly substantiated. In particular, no documents have been cited in support of it, and there is not even a suggestion of which amine(s) the Examiner may have in mind. Perhaps the Examiner is thinking of e.g. low weight alkyl amines that are relatively water soluble, and obviously not comparable to PG and BHA.

The objections in the paragraph bridging pages 20 and 21 rely on the assumption that all antioxidants and preservatives are compatible equivalents. As noted above, the attached revised Declaration supports applicant's argument that this assumption is not sound, and so these objections should be withdrawn.

In the central paragraph on page 21 the Examiner maintains that it is obvious to decrease the pH of the sodium bicarbonate-containing compositions of US 5,853,748, after adding PG or BHA, and states that it would not take a lot of other agents to do this. The Applicant simply cannot accept this, not least for the following reasons.

Bicarbonate (particularly at the level used in '748) is known as a strong buffer at its buffering pH (7-9), and by definition it would require a large amount of acid to change the pH significantly. Upon doing so, the bicarbonate ion would be displaced, leading to uncontrolled evolution of carbon dioxide, which is the last thing one would want in a pharmaceutical formulation. One would also end up with a formulation which would have significantly less bicarbonate (perhaps even none) so that one could argue that there was no point in starting with

'748 in the first place, in which case its citing as prior art is inappropriate. The concentration of bicarbonate in the '748 formulation works out at 0.1 M after dissolution, and the table in column 4 of '748 shows that even a strong buffer like MES (morpholino ethane sulphonic acid), at 50mM is unable to take it below pH 7.5. Accordingly, the assertion that it would be obvious to decrease the pH of the '748 compositions should be withdrawn.

In the final sentence in section 19 the Examiner argues that a macromolecule and non-conjugated bile acid or salt might already form a soluble formulation without any PG/BHA. In this regard the Examiner's attention is drawn to Example 6 of the present application, which gives *in vivo* data to prove the superior efficacy of compositions wherein an additive as defined in claim 1 is present.

Objection to the references to analogues, derivatives, etc in claims 9 to 11 and 19 to 21

There seems to be two strands to the objection, namely (i) it is not clear which derivatives, analogues, etc are covered, and (ii) the scope of the Examples in the application do not justify the inclusion of the analogues, derivatives, etc covered by these claims. These different strands (i) and (ii) are discussed separately below.

(i) In the response dated 5 November 2008 the Applicant argued that any skilled person would understand what is meant by the references to analogues, derivatives, etc (see pages 13 and 14 thereof). As an example, the Applicant provided an extract for insulin from the Merck index in support. In reply the Examiner has focussed instead on calcitonin, growth hormone and parathyroid hormone. Extracts from the Merck index for these other polypeptides are now therefore attached. As is evident from these extracts, the analogues and derivatives of these macromolecules are also a matter of public record, just as is the case with insulin.

Further, the Applicant takes issue with the Examiner's calculations in the discussion bridging pages 8 and 9 of the Office Action. The Examiner suggests that there are $93^{20} = 2.3 \times 10^{39}$ possible derivatives of human calcitonin. It seems this calculation is intended to highlight the number of different polypeptides with 93 residues that could theoretically exist.

This calculation is believed to be misleading. Firstly, independent claims 1 and 26 require the macromolecule to be active, and so only active derivatives and analogues would be covered by claims 9 to 11 and 19 to 21, because these claims depend on claims 1 and 26. Only a

small fraction of the huge number of alleged derivatives contemplated by the Examiner would be active.

Secondly, nearly all of the polypeptides included in the Examiner's calculation have not even a single residue in common with human calcitonin and so cannot be considered to be analogues or derivatives of it. Similar considerations apply to the other calculations on pages 9 and 11 of the Office Action. In this regard, online extracts for "derivative" and "analogue" taken from The American Heritage® Dictionary are attached. Thus, a "derivative" contains essential elements of the parent compound, and an "analogue" is a structural derivative, often differing by just a single element. Clearly the number of derivatives and analogues referred to in claims 9 to 11 and 19 to 21 is nowhere near the vast numbers calculated by the Examiner.

Notwithstanding the above comments, the Examiner's attention is drawn to the fact that the USPTO has routinely granted US patents for applications with claims containing references to "analogues" and "derivatives" of active macromolecules. By way of Example, the Applicant attaches copies of a selection of recently granted US patents spanning a range of years, namely those set out in the following table.

US Patent	Publication Date	Relevant claim	Relevant phrase in the relevant claim as granted by the USPTO
US 5,849,700	Dec. 15, 1998	15	"...growth hormone or a derivative thereof..."
US 5,891,671	Apr. 6, 1999	11	"...human parathyroid hormone or a derivative having the biological activity of human parathyroid hormone..."
US 5,849,704	Dec. 15, 1998	1	"...growth hormone or a derivative thereof..."
US 7,446,091	Nov. 4, 2008	1	"...insulin, an insulin analogue, an active derivative of insulin or an insulin analogue..."
US 7,491,187	Feb. 17, 2009	12	"...insulin, an insulin analogue, an active derivative of insulin or a monomeric human insulin analogue."

It is apparently the established practice of the USPTO to grant patents with claims referring to analogues and/or derivatives of active macromolecules. Accordingly, based on the principle of legitimate expectations it is unfair and improper for the present Examiner to depart from this practice.

(ii) The second strand of the objection is that the Examples in the application do not justify the inclusion of analogues and derivatives in claims 9 to 11 and 19 to 21.

Firstly, it is believed that this objection should fall away once the Examiner has realized that the huge numbers calculated on pages 9 and 11 of the Office Action do not represent the number of analogues and derivatives covered by these claims.

Secondly, the Examiner is reminded that the application as filed included data showing efficacy with two completely different macromolecules, namely insulin and calcitonin. On this basis the Applicant truly believes that the invention would also work with any of the analogues and derivatives referred to in claims 9 to 11 and 19 to 21. If the Examiner is contemplating maintaining this objection, the Applicant respectfully requests that the Examiner identifies which particular analogue(s) or derivative(s) mentioned in claims 9 to 11 and 19 to 21 she believes would not work (i.e. the absorption of which would not be enhanced due to PG/BHA improving bile salt solubility).

It is believed that all of the Examiner's objections have now been addressed. Favorable reconsideration of this application is respectfully requested.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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‹ analogous analogue computer ›

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The American Heritage® Dictionary of the English Language: Fourth Edition. 2000.

analogue

SYLLABICATION: an·a·logue

PRONUNCIATION: ăn'ə-lôg', -lŏg'

VARIANT FORMS: also **an·a·log**

NOUN: **1.** Something that bears an analogy to something else: *Surimi is marketed as an analogue of crabmeat.* **2.** *Biology* An organ or structure that is similar in function to one in another kind of organism but is of dissimilar evolutionary origin. **3.** *Chemistry* A structural derivative of a parent compound that often differs from it by a single element.

ADJECTIVE: **1.** often **analog** Of, relating to, or being a device in which data are represented by continuously variable, measurable, physical quantities, such as length, width, voltage, or pressure. **2.** often **analog** *Computer Science* Of or relating to an analog computer.

ETYMOLOGY: French, analogous, analogue, from Medieval Latin *analogus*, from Greek *analogos*, proportionate. See analogous.

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‹ analogous analogue computer ›

The American Heritage® Dictionary of the English Language: Fourth Edition. 2000.

derivative

SYLLABICATION: de·riv·a·tive

PRONUNCIATION: dĭ-rĭv'ə-tĭv

ADJECTIVE: **1.** Resulting from or employing derivation: *a derivative word; a derivative process.* **2.** Copied or adapted from others: *a highly derivative prose style.*

NOUN: **1.** Something derived. **2.** *Linguistics* A word formed from another by derivation, such as *electricity* from *electric.* **3.** *Mathematics* **a.** The limiting value of the ratio of the change in a function to the corresponding change in its independent variable. **b.** The instantaneous rate of change of a function with respect to its variable. **c.** The slope of the tangent line to the graph of a function at a given point. Also called *differential coefficient, fluxion.* **4.** *Chemistry* A compound derived or obtained from another and containing essential elements of the parent substance.

OTHER FORMS: **de·riv'a·tive·ly** —ADVERB
de·riv'a·tive·ness —NOUN

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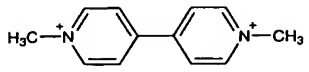
et al., Brit. J. Ind. Med. **23,** 126 (1966); D. M. Conning *et al., Brit. Med. Bull.* **25,** 245 (1969); R. D. Kimbrough, T. B. Gaines, *Toxicol. Appl. Pharmacol.* **17,** 679 (1970); J. F. Dasta, *Am. J. Hosp. Pharm.* **35,** 1368 (1978). Controversial use on marijuana plants: R. J. Smith, *Science* **199,** 861 (1978). *Review:* A. A. Akhavein, D. L. Linscott, *Residue Rev.* **23,** 97-145 (1968); A. Calderbank, P. Slade in *Herbicides: Chemistry, Degradation and Mode of Action,* P. C. Kearney, D. Kaufman, Eds. (Dekker, New York, 2nd ed., 1976) pp 501-540.



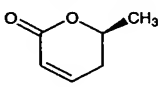
Dichloride. [1910-42-5] PP-148; Gramoxone. $C_{12}H_{14}Cl_2N_2$; mol wt 257.16. Colorless crystals, mp 300° (dec). Very sol in water, slightly sol in lower alcohols. Insol in hydrocarbons. Hydrolyzed by alkali. Inactivated by inert clays and anionic surfactants. Corrosive to metal. Non-volatile. Normal potential at 30°: −0.446 volts. LD_{50} orally in rats: 125 mg/kg (Conning).

Bismethyl sulfate. [2074-50-2] Paraquat I; PP-910. $C_{14}H_{20}N_2O_8S_2$; mol wt 408.45. Yellow solid. LD_{50} orally in male rats: 100 mg/kg (Kimbrough, Gaines).

Caution: Potential symptoms of overexposure to paraquat dichloride are irritation of eyes, skin, nose, throat, respiratory system; epistaxis; dermatitis; fingernail damage; irritation of GI tract; heart, liver, kidney damage. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 240.

USE: Herbicide. Dichloride as biological oxidation-reduction indicator.

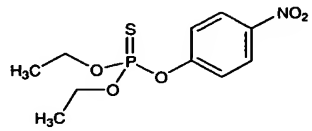
7104. Parasorbic Acid. [10048-32-5] (6*S*)-5,6-Dihydro-6-methyl-2*H*-pyran-2-one; 5-hydroxy-2-hexenoic acid lactone; δ-$\Delta^{\alpha,\beta}$-hexenolactone; 2-hexen-5,1-olide; sorbic oil. $C_6H_8O_2$; mol wt 112.13. C 64.27%, H 7.19%, O 28.54%. The sole constituent of "Vogelbeeröl", an oil obtained by steam distillation of the acidified juice of the ripe berries of the mountain ash, *Sorbus aucuparia* L., *Rosaceae:* Hofmann, *Ann.* **110,** 129 (1859); Doebner, *Ber.* **27,** 344 (1894); Kuhn, Jerchel, *Ber.* **76,** 413 (1943). Structure: *eidem, ibid.* Synthesis: Haynes, Jones, *J. Chem. Soc.* **1946,** 954; Lamberti *et al., Rec. Trav. Chim. Pays-Bas* **86,** 504 (1967). Pharmacology and acute toxicity: H. J. Meyer, R. Kretzschmar, *Arzneimittel-Forsch.* **19,** 617 (1969).



Oily liquid, sweet aromatic odor. bp_{14} 104-105°; bp_{22} 119-123°. n_D^{25} 1.4682. d_4^{18} 1.079. $[\alpha]_D^{18}$ +49.3°; $[\alpha]_D^{19}$ +210° (c = 2 in alc). Soluble in water; freely sol in alcohol, ether. Aq solns are neutral and turn acid on storage. LD_{50} in mice (mg/kg): 420 ±6.3 i.p.; 195 ±13.6 i.v. (Meyer, Kretzschmar).

7105. Parathion. [56-38-2] Phosphorothioic acid *O,O*-diethyl *O*-(4-nitrophenyl) ester; *O,O*-diethyl *O*-*p*-nitrophenyl phosphorothioate; diethyl-*p*-nitrophenyl monothiophosphate; DNTP; S.N.P.; E-605; AC-3422; ENT-15108; Alkron; Folidol; Fostox E; Rhodiatox; Thiophos. $C_{10}H_{14}NO_5PS$; mol wt 291.26. C 41.24%, H 4.85%, N 4.81%, O 27.47%, P 10.63%, S 11.01%. Non-systemic contact and stomach insecticide and acaricide; cholinesterase inhibitor. Prepn: Thurston, *FIAT Report 949* (1946); Coates, Topley, *BIOS Final Report 1808* (1947). See also Fletcher *et al., J. Am. Chem. Soc.* **70,** 3943 (1948). Conversion to toxic oxygen analogs: *See* Paraoxon. Toxicity study: T. B. Gaines, *Toxicol. Appl. Pharmacol.* **14,** 515 (1969). *Review:* Hall, *Advances in Chemistry Series* **1,** 150 (1950). Review of industrial syntheses: Chadwick, Watt, "Thiophosphates" in *Phosphorus and its Compounds* **vol. 2,** J. R. Van Wazer, Ed. (Interscience, New York, 1961) pp 1257-1262. Review of distribution, transport and fate in the environment: M. S. Mulla *et al., Residue Rev.* **81,** 1-159 (1981); of carcinogenic risk: *IARC Monographs* **30,** 153-181 (1983).

Pale yellow liquid. bp_{760} 375°; $bp_{0.6}$ 157-162°. mp 6°. n_D^{25} 1.5370. d_4^{25} 1.26. Vapor pressure at 20°: 3.78×10^{-5} mm Hg. Surface tension at 25°: 39.2 dynes/cm. Viscosity at 25°: 15.30 cp. Absorption spectra: Williams, *Ind. Eng. Chem.* **43,** 950 (1951). Freely sol in alcohols, esters, ethers, ketones, aromatic hydrocarbons. Practically insol in water (20 ppm), petr ether, kerosene, and the usual spray oils. Incompatible with substances having a pH higher than 7.5. LD_{50} in female, male rats (mg/kg): 3.6, 13 orally; 6.8, 21 dermally (Gaines).



Caution: Potential symptoms of overexposure are miosis; rhinorrhea; headache; tight chest, wheezing, laryngeal spasm, salivation and cyanosis; anorexia, nausea, vomiting, abdominal cramps and diarrhea; sweating; muscle fasciculation, weakness and paralysis; giddiness, confusion and ataxia; convulsions, coma; low blood pressure; cardiac irregularities; skin, eye and respiratory system irritation. *See NIOSH Pocket Guide to Chemical Hazards* (DHHS/NIOSH 97-140, 1997) p 240; *Clinical Toxicology of Commercial Products,* R. E. Gosselin *et al.,* Eds. (Williams & Wilkins, Baltimore, 5th ed., 1984) Section III, pp 336-343.

USE: Insecticide; acaricide.

7106. Parathyroid Hormone. [9002-64-6] Parathormone; PTH. Regulatory factor in the homeostatic control of calcium and phosphate metabolism, its principal sites of activity being the skeleton, kidneys, and gastrointestinal tract. Prime function is to raise plasma calcium concns. Acts synergistically with vitamin D_3 *(q.v.)* except in the kidneys where the latter causes phosphate retention. Secretion from the parathyroid gland varies inversely with serum Ca^{2+} concentrations, unlike calcitonin *(q.v.)* which is secreted in direct proportion to serum calcium levels. Structure consists of a single-chain polypeptide of 84 amino acid residues. Sequence varies slightly among mammalian species. Sequence of bovine PTH: Niall *et al., Z. Physiol. Chem.* **351,** 1586 (1970); Brewer, Ronan, *Proc. Nat. Acad. Sci. USA* **67,** 1862 (1970). Sequence of porcine PTH: O'Riordan *et al., Proc. Roy. Soc. Med.* **64,** 1263 (1971). Isoln of human PTH from parathyroid adenomas: O'Riordan *et al., Endocrinology* **89,** 234 (1971). Fragment exhibiting full biological activity consists of about 35 amino acid residues from the *N*-terminal: Potts *et al.* in *Parathyroid Hormone and Thyrocalcitonin (Calcitonin),* R. V. Talmage, L. F. Belanger, Eds. (Excerpta Medica, New York, 1968) p 44; *see* in entirety for review and special studies. Synthesis of active bovine fragment: Potts *et al., Proc. Nat. Acad. Sci. USA* **68,** 63 (1971); of human PTH (1-38): S. Funakoshi *et al.; Peptide Chem.* **18,** 223 (1980). Reviews of early literature: Potts *et al., Recent Progr. Horm. Res.* **22,** 101 (1966); Arnaud *et al., Ann. Rev. Physiol.* **29,** 349 (1967). *Reviews:* Behrens, Grinnan, *Ann. Rev. Biochem.* **38,** 83 (1969); Auerbach *et al., Recent Progr. Horm. Res.* **28,** 353 (1972); Parsons, Potts, "Physiology and Chemistry of Parathyroid Hormone" in *Clinics in Endocrinology and Metabolism,* I. MacIntyre, Ed. (Saunders, Philadelphia, 1972) pp 33-78. Biosynthetic review: J. F. Habener *et al., Recent Progr. Horm. Res.* **33,** 249 (1977).

Note: Aqueous solns of the active principles of bovine parathyroid gland have been used under the names: ***Parathorm, Para-thor-mone, Paroidin.***

THERAP CAT: Blood calcium regulator.

7107. Parbendazole. [14255-87-9] (5-Butyl-1*H*-benzimidazol-2-yl)carbamic acid methyl ester; methyl 5-butyl-2-benzimidazolecarbamate; 5-butyl-2-(carbomethoxyamino)benzimidazole; SKF-29044; Helmatac; Verminum; Worm Guard. $C_{13}H_{17}N_3O_2$; mol wt 247.29. C 63.14%, H 6.93%, N 16.99%, O 12.94%. Prepd from 4-butyl-*o*-phenylenediamine and car-

31-41 (1982). Cloning and expression of cDNA for HGH in *E. coli:* D. V. Goeddel *et al., Nature* **281,** 544 (1979); D. V. Goeddel, H. L. Heyneker, **BE 884012**; *eidem,* **US 4342832** (1980, 1982 both to Genentech); in mammalian cells: G. N. Pavakis *et al., Proc. Nat. Acad. Sci. USA* **78,** 7398 (1981). Purification and bioactivity of recombinant HGH: K. C. Olson *et al., Nature* **293,** 408 (1981). Clinical comparison of natural and recombinant HGH: R. L. Hintz *et al., Lancet* **1,** 1276 (1982). Use of recombinant bovine GH to increase milk production in cows: D. E. Bauman *et al., J. Dairy Sci.* **68,** 1352 (1985). Discussion of use of recombinant GH in applied animal agriculture: J. L. Burton, B. W. McBride, *J. Agric. Ethics* **2,** 129-159 (1989). Review of GH gene studies: D. D. Moore *et al., Recent Progr. Horm. Res.* **38,** 197-225 (1982). Review of bioregulation of HGH secretion: D. G. Johnston *et al., J. Roy. Soc. Med.* **78,** 319-327 (1985); of mechanism of action on target cells: O. G. P. Isaksson *et al., Ann. Rev. Physiol.* **47,** 483-499 (1985). Symposium on pharmacology and clinical efficacy: *Hormone Research* **33,** Suppl. 4, 1-107 (1990). Books: *Growth and Growth Hormone,* A. Pecile, E. Muller, Eds. (Excerpta Medica, Amsterdam, 1972); *Human Growth Hormone and Gonadotrophins in Health and Disease,* P. Franchimont, H. Burger, Eds. (Elsevier, New York, 1975) 494 pp; *Growth Hormone and Other Biologically Active Peptides,* A. Pecile, E. Muller, Eds. (Elsevier, New York, 1980); *Evaluation of Growth Hormone Secretion,* Z. Laron, O. Butenandt, Eds. (S. Karger, New York, 1983); *Use of Somatotropin in Livestock Production,* K. Sejrsen *et al.,* Eds. (Elsevier, New York, 1989).

Human growth hormone. [12629-01-5] HGH; somatropin; CB-311; Asellacrin; Crescormon; Genotropin; Grorm; Humatrope; Nanormon; Norditropin; Nutropin; Saizen; Umatrope. $C_{990}H_{1529}N_{263}O_{299}S_7$; mol wt 22124.12. A single polypeptide chain of 191 amino acids having a molecular weight of 22,124. Isoelectric point 4.9. $[\alpha]^{25}$ −38.7° (0.1*M* acetic acid).

Methionyl human growth hormone. [82030-87-3] Somatrem; met-HGH; Protropin; Somatonorm. $C_{995}H_{1537}N_{263}O_{301}S_8$; mol wt 22256.30. Produced in bacteria from recombinant DNA. Contains the complete amino acid sequence of the natural hormone plus an additional *N*-terminal methionine.

Bovine somatotropin. One of the four naturally occurring molecular variants is known as ***somavubove***, $C_{976}H_{1533}N_{265}O_{286}S_8$. Several variants have been produced by recombinant DNA technology: ***somagrebove***, $C_{987}H_{1550}N_{268}O_{291}S_9$, ***CL-291894***, ***Quest***; ***sometribove***, $C_{978}H_{1537}N_{265}O_{286}S_9$; ***somidobove***, $C_{1020}H_{1596}N_{274}O_{302}S_9$, ***EL-349***, ***LY-177837***, ***Optiflex***.

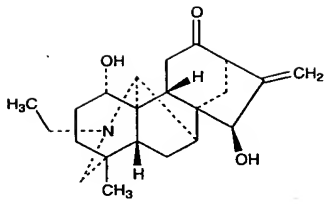
Porcine somatotropin. Somacton. Several variants have been produced by recombinant DNA technology: ***somalapor***, $C_{977}H_{1527}N_{265}O_{287}S_7$; ***somenopor***, $C_{938}H_{1469}N_{255}O_{275}S_7$; ***sometripor***, $C_{979}H_{1527}N_{265}O_{287}S_8$; ***somfasepor***, $C_{938}H_{1465}N_{257}O_{278}S_6$, ***Grolean***, ***Leanstar***.

THERAP CAT: Growth stimulant.

THERAP CAT (VET): Growth stimulant. Bovine somatotropin as galactopoietic.

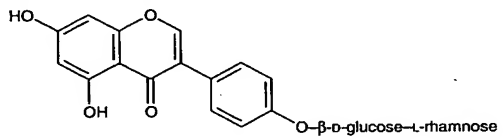
8790. Songorine. [509-24-0] (1α,15β)-21-Ethyl-1,15-dihydroxy-4-methyl-16-methylene-7,20-cycloveatchan-12-one; napellonine; zongorine. $C_{22}H_{31}NO_3$; mol wt 357.49. C 73.91%, H 8.74%, N 3.92%, O 13.43%. From *Aconitum songoricum* Popov, *Ranunculaceae:* Yunusov, *J. Gen. Chem. USSR* **18,** 515 (1948); Kuzovkov, *ibid.* **23,** 504 (1953); **25,** 2006 (1955). Identity with napellonine: Kuzovkov, *Zh. Obshch. Khim.* **28,** 2283 (1958); **29,** 1728 (1959). Structure: Sugasawa, *Chem. Pharm. Bull.* **9,** 889, 897 (1961). Absolute configuration: Okamoto *et al., ibid.* **13,** 1270 (1965). Synthesis of the aromatic intermediate: Wiesner *et al., Can. J. Chem.* **51,** 3978 (1973). Pharmacology: Sadritdinov, *Farmakol. Alk.* No. 312 (1965), *C.A.* **66,** 93772d (1967). Mass spectra data: Yunusov *et al., Khim. Prir. Soedin.* **6,** 101 (1970), *C.A.* **73,** 131178u (1970). Pharmacology and toxicity data: N. G. Bisset, *J. Ethnopharmacol.* **4,** 247-336 (1981).

Crystals, mp 201-202°. $[\alpha]_D^{20}$ −135.4°. uv max: 290 nm (log ε 2.6). LD_{50} in mice (mg/kg): 1575 orally, 630 s.c., 485 i.p., 142.5 i.v.; in rats (mg/kg): 407.5 i.p. (Bisset).



Hydrochloride. Crystals, mp 257-258°. $[\alpha]_D^{20}$ −114° (c = 2 in water).

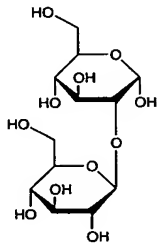
8791. Sophorabioside. [2945-88-2] 3-[4-[[2-*O*-(6-Deoxy-α-L-mannopyranosyl)-β-D-glucopyranosyl]oxy]phenyl]-5,-7-dihydroxy-4*H*-1-benzopyran-4-one; genistein-4′-glucosidorhamnoside. $C_{27}H_{30}O_{14}$; mol wt 578.52. C 56.05%, H 5.23%, O 38.72%. From fruits of *Sophora japonica* L., *Leguminosae.* Isoln and structure: Zemplén, Bognár, *Ber.* **75B,** 482 (1942). The biose is not identical with rutinose.



The anhydr substance mp 248° (slight decompn). $[\alpha]_D^{19}$ −73° (0.27 g in 10 ml pyridine). Freely sol in pyridine; sol in hot alcohol, hot acetone; slightly sol in boiling water. The alcoholic soln gives a purple color with ferric chloride.

Trihydrate. Needles from dil alcohol, mp 156-160°. The water of crystn can be removed by drying at 100° over P_2O_5 *in vacuo* for 12 hours.

8792. Sophorose. [534-46-3] 2-*O*-β-D-Glucopyranosyl-α-D-glucose. $C_{12}H_{22}O_{11}$; mol wt 342.30. C 42.11%, H 6.48%, O 51.41%. From pods of *Sophora japonica* L., *Leguminosae:* Rebaté, *Bull. Soc. Chim. France* **7,** 565 (1940); Clancy, *J. Chem. Soc.* **1960,** 4213; Clancy in *Methods in Carbohydrate Chemistry* **vol. I,** R. L. Whistler, M. L. Wolfrom, Eds. (Academic Press, New York, 1962) pp 345-349. Structure and synthesis: Coxon, Fletcher, *J. Org. Chem.* **26,** 2892 (1961); Koeppen, *Carbohyd. Res.* **7,** 410 (1968). Crystal structure: J. Ohanessian *et al., Acta Crystallogr.* **B34,** 3666 (1978).

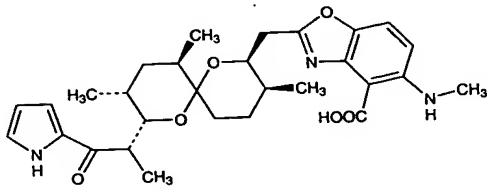


Monohydrate. Needles from 80% aq methanol, mp 196-198°. $[\alpha]_D^{18}$ +19° (c = 1.2 in water).

Octa-*O*-acetyl-β-sophorose. $C_{28}H_{38}O_{19}$. Needles from ethanol, mp 193-194°. $[\alpha]_D^{18}$ −3.2° (c = 2.5 in chloroform).

8793. Sorbic Acid. [110-44-1] (2*E*,4*E*)-2,4-Hexadienoic acid; 2-propenylacrylic acid. $C_6H_8O_2$; mol wt 112.13. C 64.27%, H 7.19%, O 28.54%. $CH_3CH{=}CHCH{=}CHCOOH$. May be obtained from berries of the mountain ash, *Sorbus aucuparia* L., *Rosaceae* where it occurs as the lactone, called parasorbic acid: Hofmann, *Ann.* **110,** 129 (1859). Synthesis by condensing crotonaldehyde and malonic acid in pyridine soln:

26200, 18200, 8200). pKa_1 6.9 in 90% DMSO. Slightly sol in water, readily sol in ethyl acetate, chloroform, methanol, DMSO. Also reported as mp 184.5-186° (Evans, 1979). LD_{50} i.p. in mice: 10 mg/kg (Gale).

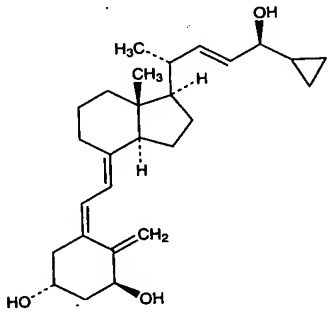


Mixed calcium-magnesium salt. Colorless crystalline solid, mp 230-250° (dec). uv max (ethanol, neutral): 202, 228, 303, 370 nm ($E^{1\%}_{1cm}$ 425, 490, 278, 109). Insol in water, pentane, hexane, heptane. Very slightly sol in methanol, DMSO. Very sol in methylene chloride, chloroform, acetone, methyl ethyl ketone, diethyl ketone, ethyl acetate.

USE: Biochemical tool used to study the role of divalent cations in various biological systems.

1640. Calcineurin. [9025-75-6] Phosphoprotein phosphatase. Ca^{2+}/calmodulin dependent ser-thr phosphatase that participates in many signalling pathways involved in gene regulation or biological responses to external stimuli in various organisms and cell types. Highly conserved heterodimer from yeast to humans comprised of a 58-69 kDa catalytic and calmodulin binding subunit A, ***calcineurin A***, and a 16-19 kDa regulatory subunit B, ***calcineurin B***. Isoln: J. H. Wang, R. Desai, *Biochem. Biophys. Res. Commun.* **72,** 926 (1976). Purification: C. B. Klee, M. H. Krinks, *Biochemistry* **17,** 120 (1978); and phosphatase activity: C. B. Klee *et al., Proc. Nat. Acad. Sci. USA* **76,** 6270 (1979). Review of early work: C. B. Klee, J. Haiech, *Ann. N.Y. Acad. Sci.* **1980,** 43-54; of role in neuronal cells and brain injury: M. Morioka *et al., Prog. Neurobiol.* **58,** 1-30 (1999). Review of structure and function: C. B. Klee *et al., J. Biol. Chem.* **273,** 13367-13370 (1998); J. Aramburu *et al., Curr. Topics Cell. Regul.* **36,** 237-295 (2000).

1641. Calcipotriene. [112965-21-6] (1α,3β,5*Z*,7*E*,22*E*,-24*S*)-24-Cyclopropyl-9,10-secochola-5,7,10(19),22-tetraene-1,3,24-triol; (1*S*,1′*E*,3*R*,5*Z*,7*E*,20*R*)-9,10-seco-20-(3′-cyclopropyl-3′-hydroxyprop-1′-enyl)-1,3-dihydroxypregna-5,7,10(19)-triene; calcipotriol; MC-903; Daivonex; Dovonex; Psorcutan. $C_{27}H_{40}O_3$; mol wt 412.60. C 78.60%, H 9.77%, O 11.63%. Vitamin D_3 analog with low calcemic activity. Prepn: M. J. Calverley, E. T. Binderup, **WO 87 00834**; *eidem*, **US 4866048** (1987, 1989 both to Leo Pharm.); M. J. Calverley, *Tetrahedron* **43,** 4609 (1987). Pharmacology: L. Binderup, E. Bramm, *Biochem. Pharmacol.* **37,** 889 (1988); P. J. Marie *et al., Bone* **11,** 171 (1990). Receptor binding: T. Valaja *et al., Biochem. Pharmacol.* **40,** 1827 (1990). Review of clinical trials in psoriasis: D. M. Ashcroft *et al., Brit. Med. J.* **320,** 963-967 (2000).



Crystals from methyl formate, mp 166-168°. uv max (96% ethanol): 264 nm (ε 17200).

THERAP CAT: Antipsoriatic.

1642. Calcitonin. [9007-12-9] Thyrocalcitonin; TCA; TCT. Calcium regulating hormone secreted from the mammalian thyroid gland and in non-mammalian species from the ultimobranchial gland. Postulation of a plasma-calcium lowering substance: Copp *et al., Endocrinology* **70,** 638 (1962). Recognition as a hormone: Hirsch *et al., ibid.* **73,** 244 (1963); of thyroid origin: Foster *et al., Nature* **202,** 1303 (1964). Overall action is to oppose the bone and renal effects of parathyroid hormone, *q.v.*; inhibits bone resorption of Ca^{2+}, with accompanying hypocalcemia and hypophosphatemia and decreased urinary Ca^{2+} concentrations. Also abolishes the osteolytic effect of toxic doses of vitamins A and D. Calcitonin is highly active biologically, *e.g.* 50 mγ/min infused into a 100 g rat leads to a significant (1 mg/100 ml) decrease in the concn of the plasma calcium within 60 min (together with a corresponding fall in plasma phosphate). Activity is destroyed by trypsin, chymotrypsin, pepsin, polyphenol oxidase; also by hydrogen peroxide oxidation, photooxidation, and treatment with *N*-bromosuccinimide. Calcitonin structures are single polypeptide chains containing 32 amino acid residues. Structure of porcine: Neher *et al., Helv. Chim. Acta* **51,** 917 (1968); Potts *et al., Proc. Nat. Acad. Sci. USA* **59,** 1321 (1968); Bell *et al., J. Am. Chem. Soc.* **90,** 2704 (1968); *eidem, Biochemistry* **9,** 1665 (1970). Synthesis of porcine: Rittel *et al., Helv. Chim. Acta* **51,** 924 (1968); Guttmann *et al., ibid.* 1155. Isoln of human calcitonin from nonpathological thyroid glands: Haymovits, Rosen, *Endocrinology* **81,** 993 (1967); from medullary carcinoma of the thyroid: Neher *et al., Nature* **220,** 984 (1968); *Helv. Chim. Acta* **51,** 1738 (1968); Neher, Riniker, **DE 1929957** (1970 to Ciba), *C.A.* **73,** 28902b (1970). Structure of human: Neher *et al., Helv. Chim. Acta* **51,** 1900 (1968). Synthesis of human: Sieber *et al., ibid.* 2057; J. Hirt *et al., Rec. Trav. Chim.* **98,** 143 (1979). Biosynthetic studies: J. W. Jacobs *et al., J. Biol. Chem.* **254,** 10600 (1979); S. G. Amara *et al., ibid.* **255,** 2645 (1980). Amino acid sequence differs among mammalian species, salmon calcitonin showing a marked difference from that of the higher vertebrae as well as a more potent biological activity. Mechanism of action: E. M. Brown, G. D. Aurbach, *Vitam. Horm. (New York)* **38,** 236 (1980). Anorectic activity in rats: W. J. Freed *et al., Science* **206,** 850 (1979). Growth inhibition of human breast cancer cells *in vitro:* Y. Iwasaki *et al., Biochem. Biophys. Res. Commun.* **110,** 235 (1983). Review of early literature: Munson, Hirsch, *Clin. Orthop.* **49,** 209 (1966). Review of isoln, structure, synthesis: Behrens, Grinnan, *Ann. Rev. Biochem.* **38,** 83 (1969); Potts *et al., Vitam. Horm. (New York)* **29,** 41 (1971). Comprehensive review: *Calcitonin, Proc. Symp. on Thyrocalcitonin and the C Cells,* S. Taylor, Ed. (Springer-Verlag, New York, 1968); Foster *et al.*, "Calcitonin" in *Clinics in Endocrinology and Metabolism,* I. MacIntyre, Ed. (W. B. Saunders, Philadelphia, 1972) pp 93-124. Review of pharmacology and therapeutic use: J. C. Stevenson, I. M. A. Evans, *Drugs* **21,** 257-272 (1981).

Calcitonin, porcine. [12321-44-7] Calcitar(e); Staporos.

Calcitonin, human synthetic. [21215-62-3] Cibacalcin.

Calcitonin, salmon synthetic. [47931-85-1] Salcatonin; Calciben; Calcimar; Calsyn; Calsynar; Catonin; Karil; Miacalcic; Miacalcin; Miadenil; Osteocalcin; Prontocalcin; Rulicalcin; Salmotonin; Stalcin; Tonocalcin. Clinical trial in postmenopausal osteoporosis: C. H. Chesnut *et al., Am. J. Med.* **109,** 267 (2000). *See also* Elcatonin.

THERAP CAT: Calcium regulator.

1643. Calcitriol. [32222-06-3] (1α,3β,5*Z*,7*E*)-9,10-Secocholesta-5,7,10(19)-triene-1,3,25-triol; 1α,25-dihydroxycholecalciferol; 1α,25-dihydroxyvitamin D_3; 1,25-DHCC; Ro-21-5535; Calcijex; Rocaltrol. $C_{27}H_{44}O_3$; mol wt 416.63. C 77.84%, H 10.64%, O 11.52%. The biologically active form of vitamin D_3 in intestinal calcium transport and bone calcium resorption: Haussler *et al., Proc. Nat. Acad. Sci. USA* **68,** 177 (1971); Raisz *et al., Science* **175,** 768 (1972). Formed by the sequential hydroxylation of vitamin D_3 at C-25 in the liver and at C-1 in the kidney: Blunt *et al., Biochemistry* **7,** 3317 (1968); Fraser, Kodicek, *Nature* **228,** 764 (1970); Norman *et al., Biochem. Biophys. Res. Commun.* **42,** 1082 (1971). Classification as a steroid hormone: Emtage *et al., Nature* **246,** 100